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The role of surgical resection in Unicentric Castleman's disease: a systematic review

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Abstract

Introduction: Castleman's disease is a rare benign lymphoproliferative disorder of unknown etiology. The disease occurs in two clinical forms with different prognoses, treatments and symptoms: a unicentric form (UCD), which is solitary, localized, and a multicentric form characterized by generalized lymphadenopathy and systemic symptoms. This article aims to review the current literature to consolidate the evidence surrounding the curative potential of surgical treatment to the unicentric type.

Material and methods: A systematic review of English-language literature was performed and databases (Medline, Pubmed, the Cochrane Database and grey literature) were searched to identify articles pertaining to the treatment of unicentric form of Castleman's disease. Each article was critiqued by two authors using a structured appraisal tool, and stratified according to the level of evidence.

Results: After application of inclusion criteria, 14 studies were included. There were no prospective randomized control studies identified. One meta-analysis including 278 patients with UCD reported that resective surgery is safe and should be considered the gold standard for treatment. Seven retrospective studies enhance this standpoint. Radiotherapy (RT) has been used in six studies with controversial results.

Conclusions: We conclude that surgical resection appears to be the most effective treatment for Unicentric Castleman's Disease of the thoracic cavity. Radiotherapy can also achieve clinical response and cure in selected patients.

Key words: castleman disease, lymphadenopathy, mediastinum, treatment outcome

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Introduction

Castleman's disease (CD) is a rare non-clonal lymph proliferative disorder of unknown etiology, which was first described as a pathologic entity in 1954 and later defined by Dr. Benjamin Castleman in 1956 [1, 2]. It is a benign tumorous process of lymphocyte cell lines, whose multiplication leads to excessive expansion of lymph nodes. This disorder has also been reported using various synonyms, which include giant lymph node hyperplasia, lymph node hamartoma, benign giant lymphoma and angiofollicular lymph node hyperplasia. Three basic histopathologic subtypes have been described: hyaline vascular (HV) (about 70-90% of individuals), plasma cell (PC), and mixed variant (MV) [3, 4]. All of these pathologic types present clinically as lymphadenopathy, with or without constitutional symptoms. There are 2 different clinical entities: the unicentric type (UCD) in which only one anatomic lymph node affected and the multicentric type characterized by generalized lymphadenopathy, constitutional symptoms, or-

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ganomegaly and more aggressive clinical course with the potential for malignant transformation [5–7]. This distinction is important for prognosis and determination of the type of therapy. The mediastinum is the most common location for localized CD, with less common extrathoracic sites being the neck, axilla, abdomen, and pelvis. Localized type is often asymptomatic at presentation and sometimes there are symptoms related to local pressure from the mass, like cough, chest pain, and dyspnea. Although the cause of CD is unknown, several theories have been formulated to account for the spectrum of associated pathologic and clinical features and various immunopathologic processes have been suggested [8–10]. The diagnosis of CD should be considered only after other more common causes of lymphadenopathy have been investigated and ruled out. The optimal treatment of Castleman's disease is unknown. However, experience with this disease has demonstrated subsets of patients for whom surgery alone appears to be definitive therapy. The surgical treatment is variable, ranging from standard thoracotomy to minimally invasive video-assisted thoracoscopy. Our principle objective is to provide a critical analysis of the literature if in patients with intrathoracic unicentric Castleman's disease is surgical resection sufficient for achieving cure and excellent long-term outcome.

Material and methods

The systematic review was conducted according to the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) including articles in English language referring to human patients at any age, gender and race with localized lesions of Castleman's disease. Studies referring to multicentric Castleman's disease, case reports letters to the editors and "Expert" opinion without critical appraisal were excluded from this study. No sample size restriction was applied during the screening for eligible studies.

The last Bibliographic search was conducted in January 16, 2018, and included the following electronic databases: Medline (PubMed), the Cochrane Database of Systematic Reviews and grey literature databases. The following medical subject heading terms were used in combination with Boolean operators (AND, OR, NOT): Giant Lymph Node Hyperplasia, Castleman's disease, unicentric, unifocal, localized, treatment, management, multicentric.

Medline/PubMed

The Medical Subject Headings (MeSH) "Giant Lymph Node Hyperplasia" and "Castleman Disease" were exploded and combined by the Boolean operator "OR" with the text word "Castleman". The text word "Castleman" was used to include in our search the recently published articles which are not MeSH indexed yet. The aforementioned search was combined by the Boolean operator "AND" with the set "unifocal OR unicentric OR localized". In order to narrow our search, we combined this set with the Boolean operator "AND" and the MeSH term "Therapeutics".

The final search string was the following: (unicentric OR unifocal OR localized) AND [("Castleman Disease"[Mesh]) OR Castleman)] AND ("Therapeutics"[Mesh]).

Cochrane database

Our search was conducted using the text words "Castleman disease" and "Giant Lymph Node Hyperplasia" returning one relevant case report.

Grey Literature

Additionally to the initial search, we scanned the following grey literature databases: The Healthcare Management Information Consortium (HMIC) database, OpenSIGLE, The National Technical Information Service (NTIS) database. Applying no restriction upon study type, our search was conducted using the text words "Castleman disease".

The search protocol was applied by two independent reviewers (AS, SM) and all disagreements were resolved by consensus with a third reviewed (NP). Following the identification of all studies retrieved from the initial search, both articles' references lists and relative articles were searched in a snowball procedure. No direct patients contact took place at any stage of our project. Corresponding authors were contacted when there was no data for the treatment applied. Data from each study was recorded into an Excel spread sheet to allow ease of comparison.

Results and discussion

The initial literature search returned 359 potentially relevant records. Following the removal of doubles, application of exclusion/inclusion criteria and review of their title and abstract, 23 reports were retrieved for full-text evaluation. Overall, 14 studies were identified for satisfying the predetermined search criteria and providing

the best available evidence. Each paper was reviewed by at least two of the authors. These are presented in Table 1. No prospective randomized control studies were identified. Ultimately, one meta-analysis including 278 patients with UCD reported that resective surgery is safe and should be considered the gold standard for treatment. Seven retrospective studies enhance this standpoint. Radiotherapy (RT) has been used in six studies with controversial results. Figure 1 displays the flow chart with the process of study selection.

Talat *et al.* [11] performed a systematic review and meta-analysis of 239 articles for a total of 404 patients with Castleman's disease between 1954 and 2009. Of 278 patients with UCD, 249 patients underwent respective surgery, 13 had combined resective surgery with immunosuppressive therapy and 16 had immunosuppressive therapy alone. Ten years' follow-up revealed 13 disease related deaths. The authors found that in patients with UCD, surgical excision is safe and should be considered the gold standard for treatment.

Ye *et al.* [12] conducted a retrospective study of 52 patients with Castleman's disease between 1999 and 2008. 48 patients had UCD and in 22 cases the lesion was located in the mediastinum. All 48 patients underwent complete surgical resections, resulting to a resolution of all symptoms and no evidence of disease recurrence during the follow-up period (22–115 months). The authors attributed that the standard therapy of UCD is surgical excision, which has been proven to be curative upon complete 'en-block' resection.

Luo *et al.* [13] in their retrospective analysis of 48 patients with Castleman's disease hospitalized between 1992 and 2012, reviewed 16 cases of UCD. In this study, all cases had abnormal chest CT: in 100% there was present hilar and or mediastinal lymphadenopathy, diffuse parenchymal lung disease (43.75%), pleural effusion (40.6%), mediastinal mass (6.25%) or hilum (3.12%) and bronchiolitis obliterans (3.12%). Open thoracic surgery was performed in all patients with UCD (1 case underwent VATS initially, then converted to open thoracic surgery) with perfect survival rates. None of the cases were treated with chemotherapy. Surgery was the preferred treatment for intrathoracic UCD masses.

Surgical excision appears to be the ideal treatment approach for UCD in five other small retrospective studies [14–18]. In total 55 patients with UCD were reviewed, all were treated with surgery (open thoracic surgery or VATS). Ko *et al.* [15] reported that radical excision of the lesion through either an open thoracotomy or VATS can produce an equally satisfying outcome with no disease recurrence during the follow-up period (range, 1 to 16 years; mean, 6.5 years). Both Zhou *et al.* [17] and Kim *et al.* [18] reported two cases of recurrence after surgical removal. For that reason, close follow-up is advised from both authors.

Five retrospective studies [19–23] and one case series with review of the literature [24] reported the use of radiotherapy in the management of UCD. Three of these studies [19–21] have shown that radiotherapy is the choice of treatment in patients who cannot undergo surgery due to unresectability. The result was significant reduction in tumor size. Keller [22] conducted a retrospective study of 81 cases with Castleman's disease (74 hyaline-vascular lesions and 7 plasma-cell lesions). Although in four patients with hyaline -vascular lesions radiotherapy was initially administered, the mass persisted and ultimately was resected. Complete surgical excision was curative in the rest of the hyaline-vascular lesion cases and in those with plasma-cell lesions. Authors concluded that in patients with unresectable UCD lesions, radiotherapy will shrink the tumor and eventually lead to regression of the symptoms. Neuhof *et al.* [23] reported the outcome in a small series of five patients with UCD that were managed either with surgery (partial excision) followed by post-operative RT or with RT alone. Patients who had the dual therapy showed no progression of the disease during the follow-up. In the 3 patients who had radiotherapy alone, two showed no progression of the disease after radiation and one suffered from serious acute and late complications (dermatitis, paraneoplastic pemphigus vulgaris, stenosis of the esophagus, left bronchus, and trachea). Accordingly, the authors reported that RT can be effective in treating UCD but a close follow-up is necessary in order to detect possible complications. Parez *et al.* [24] presented 83 pediatric patients with Castleman's disease (72 with UCD and 11 with MCD) evaluating the clinical features and the treatments' outcomes. Complete excision was performed in 70 patients with UCD. Two UCD patients underwent radiation therapy. They concluded that complete recovery occurs either by surgically resection or local RT.

The appraised systematic review/meta-analysis suggests that resective surgery with no further multimodal approach, is the gold standard regarding the management of unicentric Castleman's disease. However, there are some restrictions concerning the location of the lesion (e.g. visceral territories). In these cases, the operability and matters of technical support

Table 1. The characteristics of all included studies

Reference, study type (level of evidence)	Patient group	Outcomes	Key results	Comments
Talat *et al.* [11] Review and Meta-analysis of retrospective cohort studies	Systematic review of 239 articles of Castleman's disease between 1954 and 2009 n = 404 (UCD, n = 278; MCD, n = 126	Treatment modalities and outcomes	62/278 of patients with UCD (94.2%) underwent resective as opposed to diagnostic surgery Endoscopic techniques were used in 5 of 68 patients (7.3%) with intrathoracic disease and in 3 of 93 patients (3.2%) with intra-abdominal disease In UCD treatment: • Resective/diagnostic 262/16 (94.2%) • Resective Surgery alone (Yes/no 249/29) • Resective Surgery + immunosuppressive therapy (Yes/no 13/265) • Immunosuppressive therapy alone (Yes/no 16/262) • Death due to disease during follow-up up to 10 years (Yes/no 13/265)	In patients with UCD, it can be concluded that resective surgery is safe and should be considered the gold standard for the treatment A wedge resection may be the first step, but once a diagnosis of UCD has been established complete resection of the lymph node and/or its surrounding lymph nodes should be pursued to achieve surgical cure
Ye *et al.* [12] Retrospective cohort study	Study period: 1999–2008 at a single institution n = 52 patients (48 with UCD) and 4 with MCD)	Clinical efficacy of treatment and outcomes	22/48 UCD patients (46%) lesion located in the mediastinum All 48 patients with UCD underwent complete surgical resections No patients with UCD received chemotherapy or radiotherapy after surgical resection No recurrences have been reported after total excision within the 22–115 months of follow-up period	Standard therapy of UCD is surgical excision, which has been proven to be curative upon complete resection and en-bloc All 48 patients with UCD underwent a complete surgical resection and survived with excellent prognosis
Luo *et al.* [13] Retrospective cohort study	Study period: 1992 and 2012 n = 48 (16 cases with UCD and 32 cases with MCD)	Clinical spectrum and treatment of intrathoracic Castleman disease	All cases had significant abnormalities on their chest CT, including obvious lymphadenopathy in the hilum and/or mediastinum (100%), diffuse parenchymal lung disease (43.75%), pleural effusion (40.6%), mass in the mediastinum (6.25%) or hilum (3.12%) and bronchiolitis obliterans (3.12%) All UCD cases had thoracic surgery for diagnosis and treatment Open thoracic surgery 16/100%, VATS 1/16.67% (1 with UCD was performed VATS initially, then he was changed to open thoracic surgery) None of the cases were treated with chemotherapy and all of them were alive	Standard therapy of UCD is surgical excision
Chen *et al.* [14] Retrospective study, Single center	Study period: 1994 to 2003 n = 20 (19 with UCD, 1 with MCD)	Survival and recurrence after surgery in superficial and deep Castleman disease	11 patients had superficial disease and 9 had deep lesions 5 out of 9 deep lesions were located in the mediastinum Surgical outcome after complete resection was excellent No evidence of recurrence (disease free after a median follow up of 56 months)	Complete resection of unicentric disease certainly appeared to be curative to all patients
Ko *et al.* [15] Retrospective study, Three medical facilities	Study period: 1980–2002 n = 8 (all UCD)	Surgical outcomes (open thoracotomy, VATS)	Open thoracotomy in 6 Video-assisted thoracoscopic surgery (VATS) in 2 No tumor recurrence during follow-up (range, 1 to 16 years; mean, 6.5 years)	Radical excision of the lesion through open thoracotomy or VATS can produce an equally satisfying outcome
Mohanna *et al.* [16] Retrospective study, Two Hospitals	Study period: 1985–2003 and 1985–2001 n = 10 (9 with UCD and 1 with MCD)	Characteristics of Castleman disease and treatment outcomes	Treatment was complete surgical resection No evidence of recurrence	The treatment for localized forms of CD is complete surgical excision

Table 1. cont. The characteristics of all included studies

Reference, study type (level of evidence)	Patient group	Outcomes	Key results	Comments
Zhou *et al.* [17] Retrospective study, Single center	Study period: 2003-2008 n = 10 (8 with UCD and 2 with MCD)	Evaluate the clinical features, diagnosis and outcomes of surgical treatment	The primary treatment for patients with UCD was complete surgical resection At the time of writing (June 2011), all 10 patients were alive: 9 with no evidence of recurrence or exacerbation of CD, and 1 with symptoms of CD	UCD is usually of the hyaline vascular form and complete surgical excision of the tumor allows full recovery in most cases
Kim *et al.* [18] Retrospective study, Single center	Study period: 1981–1992 n = 7	Evaluate the clinical features, diagnosis and outcomes of surgical treatment	Lesions located in various sites: lung hilus (4 cases), posterior mediastinum (1 case), intrapulmonary fissure (1 case), and intercostal space (1 case) Surgical removal was done by conventional thoracotomy In 1 patient, recurrence was observed 9 years after surgical removal	Surgical resection and close follow-up are advised
Bowne *et al.* [19] Retrospective study, Single center	Study period: 1986–1997 n =16 (13 with UCD, 3 with MCD)	Analysis of the clinical characteristics, treatment, and outcomes	10 patients (77%) with UCD underwent a complete surgical resection 3 patients (23%) with unresectable UCD were treated with partial resection, external beam radiation therapy, and observation alone Of the 10 patients following definitive surgical resection, all remain asymptomatic and free of disease at last follow-up The 2 patients treated with partial resection and observation only are currently asymptomatic, with no further progression of disease, with a follow-up of 12 and 76 months, respectively The patient treated with radiation therapy alone demonstrated a minimal decrease in tumor size and remains without symptoms	Surgical resection for patients with the UCD is recommended Surgical removal of a unicentric mass of hyaline-vascular or hyaline -vascular/plasma cell type is curative Partial resection, radiotherapy, or observation alone may avoid the need for excessively aggressive therapy
Chronowski *et al.* [20] Retrospective study, Single center	Study period: 1988–1999 n = 21 (12 with UCD and 9 with MCD)	Analysis of treatment outcomes after surgery or radiotherapy	4 patients with unicentric disease were treated with radiotherapy alone: 2 remain alive and symptom free, 2 died of causes unrelated to Castleman disease and had no evidence of disease at last follow-up 8 patients with unicentric disease were treated with complete or partial surgical resection, and all are alive and asymptomatic Mean follow-up time: 51 months (median, 40 months)	Surgery results in excellent rates of cure in patients with unicentric Castleman disease; radiotherapy can also achieve clinical response and cure in for patients not deemed good surgical candidates or in patients who have undergone incomplete surgical excision
Uysal *et al.* [21] Retrospective study, Single center	Study period: 1980–2012 n = 11 (7 with UCD and 4 with MCD)	Analysis of treatment outcomes after surgery or radiotherapy	6 unicentric patients underwent complete surgical excision 1 unicentric patient was managed with incisional biopsy	RT is an effective treatment option for CD recurrences and sole treatment for unresectable CD
Keller *et al.* [22] Retrospective study	n = 81 (74 hyaline-vascular lesions and 7 plasma-cell lesions)	Clinical spectrum and treatment of hyaline-vascular and plasma-cell type of giant lymph node hyperplasia	Hyaline-vascular type: • complete surgical excision was curative in all the patients • RT was administered in 4 cases (in all 4 cases, the mass persisted and ultimately was resected) Plasma-cell type: • complete surgical excision was curative in all the patients	Complete surgical excision is the treatment of choice in cases of giant lymph node hyperplasia If complete excision is not possible, partial excision may be useful since regrowth of the lesion after this procedure is not expected Radiotherapy has produced little shrinkage

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Table 1. cont. The characteristics of all included studies

Reference, study type (level of evidence)	Patient group	Outcomes	Key results	Comments
Neuhof *et al.* [23] Retrospective study, Single center	Study period: 1991–2005 n = 5 (all UCD)	Analyse the responses to therapy and clinical outcomes of patients with UCD treated with RT (alone or after surgery) at a single institution	2 patients treated with surgery (partial resection) and postoperative RT showed no progression of disease during follow-up: 1 patient was in complete remission, 1 patient in partial remission Among the 3 patients treated with RT alone, 2 patients showed no progression of disease and 1 showed serious acute and late toxicities (dermatitis, paraneoplastic pemphigus vulgaris, stenosis of the esophagus, left bronchus, and trachea)	The study shows that unicentric Castleman disease is successfully treated with radiotherapy However, for detection of possible complications as pemphigus vulgaris or stenosis of the esophagus or trachea an accurate follow-up is necessary
Parez *et al.* [24] Review and Case series	Study period: 1954–1998 n = 83 (72 with UCD and 11 with MCD)	Evaluate the clinical features and outcomes of treatment in pediatric patients	Localized in the thorax in 33% cases (mediastinum: 16, hilum: 7, lung: 1) Complete excision of the mass was performed in all localized cases, except in 2 cases where radiation therapy was used 2 additional cases had spontaneous regression Complete and permanent recovery occurred when the tumor was completely resected. The 2 cases with radiation therapy also completely recovered	Complete recovery occurs when the localized tumor is completely resected or treated with local radiotherapy

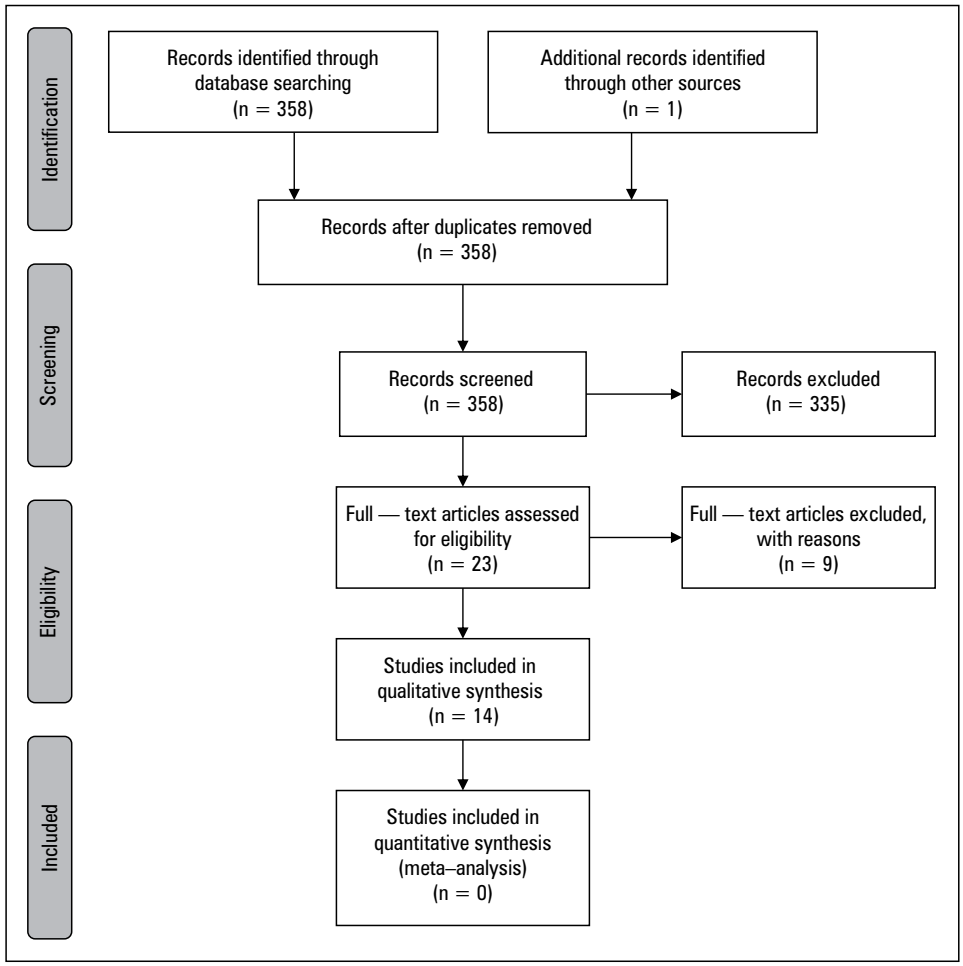

Figure 1. Flow chart with the process of study selection

affect the surgical decision making. Outcome of surgery is better in peripheral than in visceral locations. Authors performed an outcome analysis according to which, the only significant predictor for fatal outcome is failure to resect the primary involved lymph node. Moreover, they point that resection with disease free margins, minimizes the recurrence rate.

Patients with UCD who underwent surgery (had significantly high overall survival (95.3%), 3-year disease-free survival (89.7%) and 5-year disease-free survival (81.2%). In patients who failed to be treated by resective surgery there has been reported mortality of 17.6% [11]. Regarding the alternative choices in the management of UCD, radiotherapy is the only well described. Radiotherapy can also achieve clinical response and cure in patients unsuitable for surgery or in patients who have undergone incomplete surgical excision. However, there have been reported possible complications and high recurrence rates [19–24].

The authors tried to minimize publication, citation, location and outcome reporting bias, by independently conducting a systematic review in the main scientific databases under the same strict protocol. However, the main limitation of the current systematic review is the retrospective character of the retrieved studies. Several case reports and small retrospective studies have reported the characteristics and therapeutic strategies utilized in patients with UCD, and thus the design of appropriate prospective studies remains puzzling. On the other hand, due to the rarity of this disease, it is challenging to design a prospective study. The creation of an internet-based registry that could include cases from several institutions could fulfil the gap in high evidence studies which we noted. Moreover, another limitation is that only studies in English language where included in this review, and thus there is possible language bias.

Conclusion

Considering the existing data for the management on unifocal Castleman's disease, we can conclude that surgical resection appears to be the most effective treatment for resectable lesions in any organ domain. Although radiotherapy remains a therapeutic option in patients unsuitable for surgery, we would recommend caution in its application and accurate follow-up, as there have been reported possible complications and recurrence of the disease. Future research should focus on less invasive interventions, including molecular therapeutics using effective targeted agents that could target selectively Castleman's disease lesions.

Conflict of interest

The authors declare no conflict of interest.

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